CBER Stakeholders Meeting, Friday, August 28, 1998
Oakland, California

Presenter - Robert G. Miller, M.D. for
The ALS Association

The Distinguished Members of the Panel, ladies, and gentlemen:

Thank you for the opportunity to speak to this distinguished panel of the FDA and to present our concerns and suggestions regarding the implementation of the FDA Modernization Act and how it might change the approval process of biologic agents for ALS.

My name is Robert G. Miller, Director of the Norris ALS Center and Chair of Neurology at California Pacific Medical Center and Clinical Professor of Neurology at Stanford and UCSF. I am also Chair of the Medical Advisory Board of The ALS C.A.R.E. Northamerican ALS patient database, Chair of The ALS Clinical trials consortium of The World Federation of Neurology, chair of The Western ALS study group (composed of 13 academic centers conducting ALS clinical trials), and editor of the motor neuron disease section of the Cochrane Neuromuscular Disease Group. I am a clinical neurologist seeing a large number of ALS patients. I am also actively participating in several ALS clinical trials.

At this hearing today, I represent The ALS Association and I believe I also represent the entire ALS community, which includes: patient voluntary organizations, patients and families, ALS experts and pharmaceutical companies working to produce drugs for ALS.

First, I would like to briefly describe ALS and the current status of its treatment. ALS is a neurodegenerative disease that leads to death within 3 to 4 years. Lay people call ALS Lou Gehrig's disease. Patients with ALS lose the ability to move their body, to eat, to swallow, to speak, and eventually to breathe. Sometimes, a patient with ALS is described as, "a live body in a glass coffin." It is worse than the majority of cancers and AIDS, because ALS is fatal in 3 to 4 years in the majority of patients. It is estimated that up to 5,000 new patients in the U.S. are diagnosed with ALS each year. Currently, there are approximately 30,000 patients who have ALS in the United States. The impact upon patients and families is unimaginable and that to the society is also great. Only Riluzole, the first prescribable drug for ALS, is available but it has only modest effects. There is no cure and only symptomatic treatment is available. Worldwide, an increasing number of novel therapeutic

agents have been developed based on plausible hypotheses of the pathogenesis in ALS. Some are already in the pipeline. FDA has been very helpful and their commitment in developing ALS therapies is clear. In fact, as described below, the members of the FDA participated in the two Airlie House meetings for ALS diagnosis and treatment trials.

With this opportunity, I would like to present our concerns about the guideline for fast-track product review and approval and the Scientific Advisory Panel. Our concerns are specifically related to FDA questions 4,5,6 & 7 that ask about scientific expertise, timely product reviews, priorities in eliminating backlogs, and public expectations.

Because almost all neurologists agree that ALS is the most devastating of diseases, we in the ALS community believe there is no higher priority for all FDA centers, especially CBER, than to continue to expedite the review and facilitate the development of drugs for treating serious and rapidly fatal diseases such as ALS.

Thus, it is imperative that FDA Guidelines be explicit regarding fast-track diseases. The FDA should solicit from both AMA sections and specialty organizations, such as AAN, ANA, or World Federation of Neurology, a recommendation for properties of fast-track diseases. The current Guideline described in the FDA Modernization Act (Section 112) is still not specific and explicit, particularly on ALS. Therefore, we anxiously await the Agency's release for a guidance document for the section, which must be released within one year of enactment of the law (November 21, 1998).

We do not believe that the ALS drug approval process has benefited fully and fairly from accelerated approval. We are hopeful that proper implementation of this section of fast-track products will increase and expedite the availability of new therapies for ALS.

As the former FDA commissioner, Dr. Kessler stated some years ago, "when dealing with serious and life-threatening conditions, we cannot wait for all the evidence to come in." For truly life-threatening diseases such as ALS, the FDA can expedite the availability of therapies to patients in desperate need, by providing greater authority to approve drugs that strongly suggest effectiveness as stated in the Public Law. By permitting greater use of Phase IV post-approval confirmatory trials, and yet adhering to its own

standard, the FDA should be able to require substantial evidence of effectiveness. This procedure has worked well in the AIDS and terminal cancer areas, and we believe that fast-track products were intended to expand that procedure to all drugs to treat serious and life-threatening conditions, such as ALS. After all, 17 of the 20 Subpart H accelerated approvals since 1992 have been in AIDS and cancer and only 3 have been in other life-threatening conditions, according to the *Drug Information Journal*.

New guidelines for ALS clinical trials have been developed (April 1994) and recently revised (April 1998). In this context, members of the FDA, including Dr. Paul Lieber, have been most gracious to attend the World Federation of Neurology meeting and supportive of the effort of ALS clinical researchers and pharmaceutical industries for revising the ALS Diagnostic Criteria and the ALS Clinical Trials Guidelines. Therefore, the FDA team has a growing understanding of the issues in ALS clinical trials.

The FDA should consider efficacy relative to safety. Large experience with a drug such as IGF-I, which has shown minimal side effects, should weigh in heavily, even if there is only a small benefit. In particular, if two studies show safety and only one shows efficacy, in diseases such as ALS where long-term exposure is probably not an issue, we need to press ahead. An approval of such safe, yet modestly effective drugs ensures the phase IV studies for long-term efficacy. Many cancer drugs and immunosuppressive drugs for organ transplant are approved based on efficacy relative to safety. Again, ALS trials have not been treated the same as other life-threatening diseases by the FDA.

Finally, ALS has, at present, no surrogate markers as cancers and AIDS do. Although there is an urgent need for developing surrogate markers for ALS, continuous cumulative physical disability shown by quantitative muscle strength testing, pulmonary function tests, and a well-validated ALS scale, must be sufficient to evaluate the efficacy of a drug or biological product into the fast track approval process.

Next, I would like to discuss the Scientific Advisory Panel in Section 120 of the Modernization Act.

Only two drugs for ALS, Riluzole and IGF-I, have ever come before an FDA Advisory Panel and both were highly controversial and often given contentious reviews. Given the great weight that FDA places on Advisory Panel decision, it is absolutely critical that true experts in the actual disease under review be represented on these Panels.

Public Law Subsection 120 states, "two or more members who are specialists or have other expertise in the particular disease or condition for which the drug under review is proposed to be indicated." Undoubtedly the members of the Scientific Advisory Panel are the most capable and reputable members of medical community, and I respect them greatly. However, the ALS community feels that true ALS experts have not been represented within the Panel.

It was apparently difficult to invite experts who have no conflict of interest with respect to pharmaceutical companies. Nevertheless, there are senior neurologists and other ALS experts who are not involved with clinical trials or pharmaceutical companies. Again, the participation of ALS experts in Scientific Advisory Panel is imperative.

In this context, the World Federation of Neurology (WFN), and the Committee on Motor Neuron Disease can provide independent expertise in this review process. There are approximately 100 neurologists worldwide who have formed the International ALS Clinical Trial Consortium. This group has developed the ALS Clinic Trials Guidelines and has broad experience with ALS clinical trials.

One solution may be the use of ad hoc reviewers from experts in such diseases. The International ALS Clinical Trial Consortia, again may be helpful when acting as such an outside ad hoc panel.

I would like to discuss the current forum of a publicly open Scientific Advisory Panel meeting. In this forum, the patient's testimonial is allocated and is, in fact, extremely important. However, these testimonials are so powerful and highly emotional that I, personally, wonder how the panel members can make their judgement based purely on scientific grounds. On some occasions, it appeared the panel had made prior decisions, leaving patient's testimonies to have little influence. This type of forum, although extremely important, may need to be more effectively incorporated in the entire process. The FDA and the Advisory Panel should explore further options.

Next, I would like to point out a question I have as regards CDER and CBER. My confusion springs from recent experiences with IGF-1. IGF-1 is a recombinant biological product; however, the approval process adopted by CDER required two independent clinical trials. All other neurotrophic factors, such as CNTF, BDNF, or GDNF, were to be evaluated by CBER requiring only one clinical trial. These inconsistencies (requiring 2 trials at CDER) should be eliminated.

I believe that the FDA should aggressively educate patients' advocacy groups, disease specific organizations, disease experts, and the new biotech companies that have never filed their product to the FDA. The FDA needs to inform these groups of its function, process, and scope more than ever, because recent progress in therapeutics will increase drug approval applicant even exponentially.

Regarding the future direction of fast-track approval, the FDA should solicit from the disease specific groups information regarding potentially effective drugs in such disease. The FDA should proactively plan the future drug approval process for fast-track diseases and should then formalize and implement those plans.

Currently, the FDA supports some research in new drug development; however, I propose that the FDA should also fund new research for developing surrogate markers in fast-track diseases that have no surrogate markers at present. It is of great urgency to help the American people who suffer from this most devastating disease. Since the NIH budget was increased in the past year, I believe the FDA budget should echo such an increase. Without such a Federal budget increase, the FDA will not be able to meet the need of the American people.

I greatly appreciate this opportunity to present our views. Thank you very much for your attention.

Robert G. Miller and
The ALS Association